subject of an approved application or abbreviated application (hereinafter called application).

The agency has concluded that although nonoxynol 9 and octoxynol 9 kill sperm in vitro and in vivo, the spermicidal activity and resulting effectiveness of these contraceptive active ingredients cannot be considered separately from a product's vehicle. Studies show that these active ingredients lose some of their effectiveness in humans when the spermicide in final formulation is diluted by varied amounts of genital secretions during coitus. Thus, clinical studies are necessary to establish the effectiveness of the spermicide's final formulation when used in humans. (See discussion in section I.A., comment 3 of this document.) Such clinical studies would determine the influence of the potential interactions among the genital secretions, microorganisms, and contraceptive product vehicle.

The agency recognizes a need for consumers to continue to have access to OTC vaginal contraceptive drug products and to avoid disruption in the marketplace. The majority of OTC vaginal contraceptive drug products currently marketed contain nonoxynol 9. At the present time, two approved applications exist for OTC vaginal contraceptives: Delfen Contraceptive Foam (new drug application (NDA) 14-349) and Today® Sponge (NDA 18-683). The NDA for Delfen Contraceptive Foam was approved a number of years ago, and the product as currently marketed uses a different formulation from the one approved in the NDA. The manufacturer of this product will be required to provide additional information. The manufacturer of the Today[®] Sponge recently announced that it plans to discontinue production of this product. However, the firm has not indicated to FDA that it plans to withdraw its application.

Only a few vaginal contraceptive drug products contain octoxynol 9, and none have approved applications. Because the final rule for this class of OTC drug products will be effective 12 months after the date of its publication in the Federal Register, FDA strongly recommends that manufacturers of products not having an approved application consult with the agency as soon as possible concerning the content of these applications. Elsewhere in this issue of the Federal Register, the agency is announcing the availability of a guidance document that is intended to help manufacturers of vaginal contraceptive drug products develop data in support of new drug applications.

OTC vaginal contraceptive products that are marketed for use with or as part of a condom, diaphragm, or a contraceptive cervical cap will not be subject to the final rule. When labeled for use only with a device such as a condom (see 21 CFR 884.5310) diaphragm (see 21 CFR 884.5350), or cervical cap (a premarket approval application has been approved for a cervical cap for use as a barrier method of contraception, when used with a spermicidal cream or jelly), a spermicide is considered an accessory to a device. The regulation of spermicides for use only with a device will be addressed at a future date by the agency. In the interim, manufacturers of such products should direct inquiries to the Obstetrics/Gynecology Branch (HFZ-471), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 1390 Piccard Dr., Rockville, MD 20850, 301-594-1180.

The agency has determined that nonoxynol 9 and octoxynol 9 would be appropriate ingredients for an approved application. This determination is based on: (1) The findings of the Panel (nonoxynol 9 and octoxynol 9 were recommended as Category I active ingredients), and (2) the history of use of drug products with approved NDA's containing nonoxynol 9.

Applications for products containing these ingredients will not need to include preclinical data, but, instead, may refer to the Panel's report as a general basis for the safety of these ingredients. The applications will need to include the results of clinical studies that establish the effectiveness of the contraceptive ingredient in the product's final formulation. These studies to establish the effectiveness of the product's final formulation need to comply with the requirements of 21 CFR part 314. The clinical studies should contain evidence of the effectiveness of the spermicide in final formulation in normal volunteers or patients that is consistent with correct use of the product. In addition, the agency is aware that the use of either of the contraceptive ingredients addressed in this proposed rulemaking may be associated with varying degrees of vaginal irritation under certain conditions of use and it is unclear whether this may play a role in the transmission of STD's (Refs. 1 through 5). Therefore, as part of the application for approval of these products for contraceptive use, information regarding the rate of occurrence and degree of vaginal irritation should be presented. FDA encourages manufacturers to consult with the agency as soon as

possible concerning the content of these applications. Inquiries should be directed to the Division of Metabolism and Endocrine Drug Products (HFD– 510), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3490.

The Department of Health and Human Services has published the "13th Edition of Approved Drug Products with Therapeutic Equivalence Evaluations,' commonly called "the Orange Book," which identifies currently marketed products approved by FDA on the basis of safety and effectiveness data. The main criterion for the inclusion of any product in the Orange Book is that the product is the subject of an approved application that has not been withdrawn for safety or effectiveness reasons. For vaginal contraceptive drug products for which there is a previously approved listed drug product in the Orange Book, an abbreviated application may be submitted. The abbreviated application must contain information to show bioequivalence to the listed drug product. Further, the abbreviated application may contain labeling only for the claims approved for the product, i.e. a contraceptive. None of the products containing nonoxynol 9 that are listed in the Orange Book has a claim for the prevention of infectious disease. Manufacturers should consult with the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-0340, to determine the procedures for obtaining approval of abbreviated applications. For vaginal contraceptive drug products for which there is no previously approved listed drug product in the Orange Book, an abbreviated application may not be submitted. For these products, an application that includes adequate and well-controlled clinical studies of the effectiveness of the specific formulation of the vaginal contraceptive must be submitted. Manufacturers of such products should direct inquiries to the Division of Metabolism and Endocrine Drug Products, as noted above.

Both types of applications, i.e., full or abbreviated, would also have to include information on the drug product's formulation, manufacture, and quality control procedures to ensure that the applicant has the ability to manufacture a safe and effective OTC vaginal contraceptive drug product. (Also, see section I.C., comment 15 of this document.)

The agency is aware of literature reports and other data concerning the